# Decision Memo for Positron Emission Tomography (N-13 Ammonia) for Myocardial Perfusion (CAG-00165N)

## **Decision Summary**

CMS determines that the evidence is adequate to conclude that the use of N-13 ammonia PET for the evaluation of myocardial perfusion is reasonable and necessary for the diagnosis or treatment of the illness or injury or to improve the functioning of a malformed body member in the population specified.

In addition, CMS determines that the evidence is adequate to impose the following limitations:

The PET scan, whether at rest alone, or rest with stress, is performed in place of, but not in addition to, a single photon emission computed tomography (SPECT); or

The PET scan, whether at rest alone or rest with stress, is used following a SPECT that was found to be inconclusive. In these cases, the PET scan must have been considered necessary in order to determine what medical or surgical intervention is required to treat the patient. (For purposes of this requirement, an inconclusive test is a test(s) whose results are equivocal, technically uninterpretable, or discordant with a patient's other clinical data and must be documented in the beneficiary's file.

Therefore, we intend to issue a positive national coverage determination announcing the addition of coverage for N-13 ammonia PET for the evaluation of myocardial perfusion.

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### **Decision Memo**

This decision memorandum does not constitute a national coverage determination (NCD). It states CMS's intent to issue an NCD. Prior to any new or modified policy taking effect, CMS must first issue a manual instruction giving specific directions to our claims-processing contractors. That manual issuance, which includes an effective date, is the NCD. If appropriate, the Agency must also change billing and claims processing systems and issue related instructions to allow for payment. The NCD will be published in the Medicare Coverage Issues Manual. Policy changes become effective as of the date listed in the transmittal that announces the Coverage Issues Manual revision.

TO: Administrative File CAG #00165N

FROM:

Steve E. Phurrough, MD, MPA Acting Director, Coverage and Analysis Group

Anthony Norris
Health Insurance Specialist, Coverage and Analysis Group

SUBJECT: N-13 Ammonia and Positron Emission Tomography for Myocardial Perfusion

DATE: April 16, 2003
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This memo serves four purposes: (1) briefly outlines the assessment of coronary artery disease and congestive heart failure using N-13 ammonia and positron emission tomography; (2) reviews the history of Medicare's coverage process on the use of PET for myocardial perfusion; (3) presents and analyzes the relevant scientific literature assessing the clinical effectiveness of N-13 ammonia PET and comparing it to Rubidium-82 (Rb-82) for the detection of myocardial perfusion; (4) announces our intention to issue an NCD revising CIM 50-36 and delineates the reasons for making a positive coverage determination for the use of N-13 ammonia PET for assessing myocardial perfusion.

#### **Clinical Background**

Cardiovascular disease (CVD) is a broad term encompassing several conditions, such as, coronary artery disease (CAD), congestive heart failure (CHF), and stroke. CVD is the number one cause of death in the United States, claiming 949,619 lives in 1998. Of that total, 459,841 deaths were attributable to CAD. Eighty-five percent of the people who die of CAD are age 65 or older and, thus, may be Medicare beneficiaries.

The incidence of CHF in Medicare beneficiaries approaches 10 per 1000. Patients with this disease are at risk for increased morbidity and mortality. The mortality of this subset of patients correlates with the severity of left ventricular dysfunction. Annual mortality in patients with left ventricular ejection fraction (LVEF) 31%-35% is approximately 9%, with LVEF 26%-30% is 12%, and with LVEF less than 25% is 24%.<sup>3</sup>

The ultimate goal of CHF management is to maximize the amount of viable, functioning myocardium. Medical therapy is used to optimize the functioning of all viable myocardium. Interventional therapy attempts to improve the function of the myocardium by identifying areas of viable myocardium that are inadequately perfused and providing revascularization therapy (bypass grafting, angioplasty and stenting).

Two types of diagnostic tests are widely used to determine the amount of viable, functioning myocardium a patient has. Myocardial *perfusion* studies assess cardiac ischemia by defining the distribution of blood flow to the myocardium. This has typically been done angiographically and that remains the gold standard. Nuclear imaging studies have been developed that measure relative regional distribution of isotope uptake in the myocardium at rest, under cardiovascular stress or under both conditions. However, determining that areas of underperfusion exist does not resolve the question as to whether a revascularization procedure will improve the functioning of the area underperfused.

Areas of the myocardium that are underperfused could be viable myocardium that will improve with increased perfusion or infarcted scar tissue that will not respond to reperfusion. Myocardial *viability* studies assess the functional capability of myocardium by measuring myocardial cell uptake of radioisotopes. Areas of decreased isotope uptake would correspond to hypokinetic areas on angiograms.

When these studies are combined in a patient with known cardiac ischemia and/or infarction, a clinician can determine the extent of viable cardiac tissue as opposed to infarcted, non-viable tissue. An area of ischemic, viable myocardial wall will show a mismatch between the blood flow to the myocardium and cell uptake within the myocardium. Regions showing deficits in both perfusion and uptakematching resultscan be considered non-viable (e.g., scar). These studies thus provide valuable information to the clinician in planning appropriate therapy.

Nuclear imaging for myocardial perfusion and viability was initially and continues to be performed using technetium and thallium as the radioisotope with single photon emission computed tomography (SPECT). Positron emission tomography with F-18 flurodeoxyglucose (FDG PET) has also been shown to be helpful and potentially more accurate in evaluating myocardial viability.

Rubidium-82 positron emission tomography (Rb-82 PET) has demonstrated efficacy in identifying myocardial perfusion defects and is commonly used in place of SPECT or after an inconclusive SPECT. N-13 ammonia PET has had published reports in the literature since 1970 for evaluation of myocardial perfusion. Because N-13 is a radionuclide of a natural constituent of ammonia, as opposed to some of the other isotopes, it is expected to participate in the normal physiological uptake of ammonia. N-13 ammonia is highly extractable from the circulation into myocardial cells where it is rapidly metabolized. This property may provide information on microperfusion, in addition to conveying anatomical information (patency or occlusion) about larger vessels. Both Rb-82 and N-13 ammonia PET are currently combined with FDG PET to provide the matching analysis between perfusion and viability.

Access to nuclear imaging is a crucial issue for Medicare beneficiaries. SPECT is widely available throughout the US. PET imaging is still in its early diffusion phase and many communities lack this technology. In addition, Rb-82 has a different manufacturing process from FDG and N-13 ammonia. Rb-82 is generator-produced while the other two are produced in a cyclotron. All three isotopes have a relatively short half-life, necessitating local production. Therefore, using Rb-82 and FDG requires a community to support both technologies.

History of Medicare's Coverage on PET for Myocardial Perfusion

On March 14, 1995, CMS began covering PET for myocardial perfusion using the radiopharmaceutical Rb-82. In the evaluation of myocardial perfusion, FDG PET is covered as a primary or initial diagnostic study, or following an inconclusive SPECT, prior to revascularization. SPECT may not be used following an inconclusive PET.<sup>4</sup>

In addition, in 1998, CMS began covering the use of FDG PET or SPECT for the evaluation of myocardial viability<sup>5</sup>. It also can be used as an initial study or following a SPECT that was inconclusive.

#### **Timeline of Recent Activity**

September CMS elected to begin a national coverage determination process following the receipt of a formal request from 4, 2002 R. Edward Coleman, MD, Director, Division of Nuclear Medicine, Duke University Medical Center, "for a national coverage decision for N-13 ammonia for PET imaging of the myocardium under rest and/or pharmacologic stress conditions to evaluate myocardial perfusion in patients with suspected or existing coronary disease."

#### Food and Drug Administration (FDA) Status

The FDA has approved the new drug application for N-13 ammonia determining that it is safe and effective in PET imaging in patients with CAD "for evaluation of myocardial blood flow.6"

Benefit Category
In the preamble to a final rule published on November 1, 2002, CMS noted:
Section 1861(t)(1) provides that the terms drugs and biologicals "include only such drugs (including contrast agents) and biologicals, respectively, as are included (or approved for inclusion) in [one of several pharmacopoeias] (except for any drugs and biologicals unfavorably evaluated therein), or as are approved by the pharmacy and drug therapeutics committee (or equivalent committee) of the medical staff of the hospital furnishing such drugs and biologicals for use in such hospital." A careful reading of this statutory language convinces us that inclusion of an item in, for example, the USPDI does not necessarily mean that the item is a drug or biological. Inclusion in such reference (or approval by a hospital committee) is a necessary condition for us to call a product a drug or biological, but it is not enough. Rather, if we are to call a product a drug or a biological for our purposes, CMS must still make its own determination that the product is a drug or biological <sup>7</sup>
The appropriate benefit category for all diagnostic radiopharmaceuticals is 1861(s)(3). We will consider neither diagnostic nor therapeutic radiopharmaceuticals to be drugs as described in section 1861(t).8

**Summary of Evidence** 

To evaluate the diagnostic accuracy of N-13 ammonia PET, the performance characteristics of N-13 ammonia	PET	need
to be determined directly in the evaluation of myocardial perfusion or in comparison to Rb-82 PET.		

We obtained the evidence for this determination through several sources:

- A large, systematic review of the literature performed by the FDA, dated February 18, 1999, used as the basis for FDA approval of N-13 ammonia.<sup>9</sup>
- 2. A literature review with evidence tables submitted as part of the formal request package by R. Edward Coleman, MD.<sup>10</sup>
- 3. An OVID MEDLINE search.

#### FDA Systematic Review

The FDA systematic review is the most comprehensive review identified. Search criteria included: studies published from January 1990 to July 1, 1998 identified as human clinical trials with N-13 ammonia PET, written in English, found by searching on-line databases of Medline, Cancerlit, Derwent Drug File, Biosis Preview, International Pharmacology Abstracts and Embase. Review articles on N-13 ammonia PET imaging were identified using the same criteria in the Cochrane Database for Systemic Reviews and Cochrane Controlled Trials Register. Finally, FDA solicited references from the PET community on N-13 ammonia PET from any time period published in peer-reviewed journals.

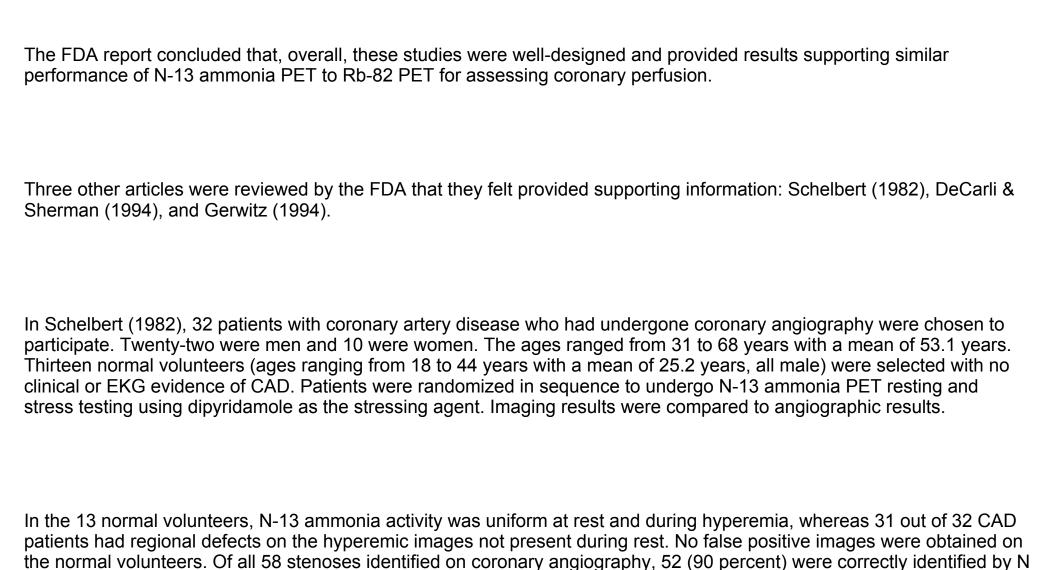
n all, 17 articles were included in the review of effectiveness. Two articles were reviewed as being adequate and well-controlled published studies, 3 were reviewed as controlled studies that were supportive, and 9 were reviewed as other published studies that had supporting information.
Gould (1986) and Demer (1989) were the two adequate, well-controlled studies that allowed assessment of the effectiveness by meeting the following criteria:
<ul> <li>There was comparison between N-13 ammonia PET and an accepted "truth" standard of coronary perfusioncoronar angiography;</li> <li>The study population was prospectively enrolled;</li> <li>The entry criteria defined the target clinical population in which N-13 ammonia PET was intended to be used;</li> <li>There were clearly defined endpoints;</li> <li>Detailed data on findings were presented; and</li> <li>There were procedures to minimize interpretation bias, such as masking (also referred to as blinding) and randomization, when flow measurement was not performed quantitatively.</li> </ul>
The first article, Gould (1986), is the initial report of findings and the second article, Demer (1989), is the comprehensive report that includes data from the first study.
Γhe strengths of these studies include:

- The proper population for PET imaging was studied; i.e., those who had indications of possible CAD and were undergoing cardiac catheterization.
- It was a prospective collection of patients.
- There were subjects with normal coronary anatomy included in the selection.
- Although small in sample size, the study had the appropriate enrollment criteria to encompass a board spectrum of the disease, patients with possible CAD.
- PET imaging was compared to an accepted standard, cardiac angiography.
- The interpreting physicians were masked and read images of the same patient three times.

#### Weakness in these studies included:

- The first study lacked information on inter-reader variability, whether images were read independently, the frequency of disagreement of PET interpretations, and dispute resolution. This was corrected in the second study.
- Results were not stratified by radiopharmaceutical (Rb-82 versus N-13 ammonia). However, the study did mention, "There was no difference in sensitivity and specificity between the two tracers in this small number of patients." This implies that data was analyzed to support this statement, but was not published.
- There were a small number of subjects.

In Demer (1989), 111 patients received PET perfusion imaging with N-13 ammonia and the remaining 82 patients with Rb-82. Thus, the two radiopharmaceuticals were not compared to each other in the same patients. Therefore, one cannot compare the two radiopharmaceuticals directly but must draw conclusions from the performance characteristics determined separately. Two independent readers, who were blinded to clinical data, visually interpreted rest and stress images. Arteriographic stenosis flow reserve (SFR) was compared to PET defect severity, with 105/111 (5 false negative and 1 false positive) N-13 ammonia images and 79/82 (2 false negative and 1 false positive) Rb-82 images providing findings consistent with arteriographic results. These ratios were not significantly different (p=0.73), and qualitative similarities were also noted between both tracer images. Such data suggest equivalent performance between the tracers.



-13 ammonia PET. This results in a sensitivity of 97% and a specificity of 100% (assuming all the controls did not have

coronary artery disease).

In summary, this was a study comparing PET and angiography readings in retrospectively selected patients with known CAD and normal volunteers. The strength of the study lies in its consistent results across two independent readers, despite having a subjective, dichotomous endpoint: normal or abnormal homogeneity of radiopharmaceutical activity. The correlation between PET results and angiography with respect to patients and vessels identified as diseased is reproduced from Gould (1986) and Demer (1989). The FDA concluded that this study supports the utility of N-13 ammonia PET for assessing myocardial perfusion in the evaluation of CAD.

The other two studies, DiCarli & Sherman (1994) and Gerwitz (1994), tested the hypothesis that microperfusion seen on N-13 ammonia PET would be more diagnostic than angiographic information (N-13 ammonia PET can identify perfusion at lower flow levels than angiography). They did not directly address the performance characteristics of N-13 ammonia PET directly and, therefore, not directly on point for this determination. The FDA did believe they were well-designed studies supporting their approval deliberations.

Laubenbacher (1993), DiCarli & Davidson (1994), Gould (1994), Beanlands (1995), Czernin (1995), Gould (1995), Sambuceti (1995), Soufer (1995), and Haas (1997) were nine other studies evaluated by this review that, although having differing hypotheses and design, did provide supporting information of N-13 ammonia PET efficacy.

The FDA systematic review concluded that the well-controlled studies of Gould (1986) and Demer (1989) along with corroborating data from other studies permit an estimate of N-13 ammonia PET's performance characteristics that support its utility in the assessment of myocardial perfusion in patients with coronary artery disease.

#### Requestor's Review

The requestor submitted a large volume of literature with evidence tables and a summary. This was not a systematic review and the strengths and weaknesses of the studies were not assessed. Only one article met the criteria of testing against a gold standard, Schelbert (1982). The remainder evaluated differing hypotheses for the use of N-13 ammonia PET. The summary specified an overall approximate sensitivity of 90% and a specificity of 90% though the method of calculating them was not given.

#### CMS Evidentiary Review

CMS performed a search for English language and human subjects only, using the keywords "N-13 Ammonia" and "Rb-82" and "SPECT" and "Myocardial Perfusion" for publication dates after 1990. Review of reference lists in these articles yielded additional articles, including those predating 1990. Review articles, articles without a "gold standard" for comparison, and articles with a hypothesis not assessing perfusion in CAD were excluded.

Only five articles met our criteria. All predated 1990. The acceptance of N-13 ammonia as a nuclear imaging tracer in clinical practice before 1990 has resulted in subsequent studies addressing other issues to include:

- Ability of N-13 ammonia PET to predict outcomes in high risk patients;
- Predicting recovery from acute myocardial injury;
- Use in diseases other than CAD; e.g. hypertrophic cardiomyopathy;

- Differentiating ischemia and infarction acutely; and
- Quantifying myocardial flow by region.

Studies that directly addressed the sensitivity and specificity of N-13 ammonia PET as a diagnostic test for myocardial perfusion are summarized in the evidence table below. Angiographic findings were used as the gold standard in each of these studies. Sensitivities ranged from 88-97% and specificities from 90-100%.

Author/Year	Subjects	Gold Standard	Sensitivity	Specificity	Stress Source
Schelbert (1982) <sup>11</sup>	32 with documented coronary artery disease (CAD) and 13 normal	Angiography	31/32 (97%) with abnormal PET:	13/13 (100%)	Dipyridamole-induced coronary hyperemia
	volunteers		One false negative		
Yonekura (1987) <sup>12</sup>	40 patients with CAD by angiography; 26 with prior MI	Angiography	After exercise, 37/38 (97%) of patients with CAD.	12/12 (100%)	Exercise

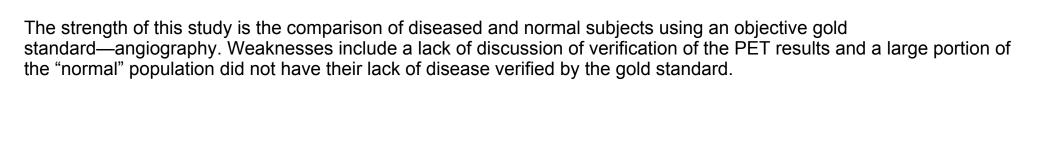
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Author/Year	Subjects	Gold Standard	Sensitivity	Specificity	Stress Source
	All 40 had rest PET studies; only 38 had exercise studies (2 became unstable).		67/75 (89%) of all stenosed vessels		
	20 normal volunteers; 9 with atypical chest pain and normal angiography and 11 w/o clinical, ECG or physical evidence of CAD. 8 were used to establish minimum limits for normal values. Only 12 were studied.				
Tamaki (1988) <sup>13</sup>		Angiography		3/3 (100%) for angiographically normal patients	Exercise

Author/Year	Subjects	Gold Standard	Sensitivity	Specificity	Stress Source
	51 patients referred for coronary angiography without further elaboration of clinical presentation, other than 38 had history of myocardial infarction		47/48 (97%) for patients with abnormal angiograms.  80/91 (88%) of all stenosed vessels.	56/62 arteries (90%) for vessels without disease	

Schelbert (1982) has been discussed above.

Yonekura (1987) enrolled 60 patients in a study to assess the accuracy of N-13 ammonia PET in diagnosing CAD as compared to an angiographic gold standard. Forty patients (36 men, 4 women; average 52, range 34 – 72) with angiographically demonstrated disease were selected and underwent rest and exercise PET studies (2 patients with 3 vessel disease became unstable and did not progress to the exercise study). The 20 normal volunteers (18 men, 2 women; average age 45, range 25 – 65) included 9 who had angiography for atypical chest pain. The remaining 11 had no evidence of CAD by clinical and ECG exam. They did not undergo angiography. Eight of the 20 normal subjects studies were limited to determination of minimum limits of the normal values.



The results demonstrated a sensitivity of 97% in identifying patients with CAD and 89% in identifying diseased vessels. If one assumes that all the normal patients were disease free, then the sensitivity for identifying patients without CAD was 100%.

Tamaki (1988) studied 51 patients who were referred for coronary angiography and performed both stress thallium SPECT and stress N-13 ammonia PET. Gender was not specified. The age ranged from 34 to 71 with a mean of 56.1. Thirty-eight patients had a history of myocardial infarction. The angiograms and nuclear images were all independently interpreted by three experienced observers without knowledge of patient conditions or results of other tests. Though this was a comparison of N-13 ammonia PET to thallium SPECT, the results of the N-13 ammonia PET data are illustrative.

This is a well-designed study. Appropriate patients are selected, a gold standard is used, and masking appears appropriate. A weakness is the lack of discussion of patient selection.

The results of the N-13 ammonia PET data demonstrates a sensitivity of 98% in identifying patients with CAD and a sensitivity of 88% in identifying diseased vessels. Three patients had normal angiograms and all three had a negative N-13 ammonia PET for a specificity of 100% for patients with disease. Specificity was 90% for diseased vessels.

The results for the thallium SPECT were similar, demonstrating a sensitivity of 96% in identifying patients with CAD and 81% in identifying diseased vessels. These results were statistically not significantly different from the N-13 ammonia PET results. The three normal angiograms also had negative SPECT results.

With respect to the comparative performance of N-13 ammonia and Rb-82, only two articles were obtained. These are the studies by Gould (1986) and Demer (1989) discussed above.

CMS' search found no new literature since the 1995 coverage determinations on RB-82 addressing the comparison of Rb-82 and SPECT. Similarly, no recent evidence was found comparing N-13 ammonia PET and SPECT.

#### Position Statements

CMS received a joint letter from the American Society of Nuclear Cardiology (ASNC) and the American College of Cardiology (ACC) providing support in favor of Medicare coverage of N-13 ammonia as a myocardial perfusion tracer. This letter critically reviewed the literature, evaluating many of the articles CMS reviewed. In its review, it listed sensitivities of 94-98% and specificities of 95-100% for the detection of CAD.

#### **Expert Opinions and Public Comment**

CMS received a letter from the Kansas University Medical Center during the public comment period and informally consulted several clinical experts<sup>14</sup> in the course of this review. They were uniform in their opinion that N-13 ammonia is equal to if not superior to Rb-82 for PET myocardial perfusion imaging and has certain advantages over Rb-82.

#### **CMS Analysis**

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A).

CMS has issued regulations pertaining to the coverage of diagnostic tests under the Part B program. Those rules provide that, except for a few exceptions, diagnostic tests must be ordered by the physician who treats the beneficiary for a specific medical problem and the physician must use the results in the management of the beneficiary's specific medical problem (42 C.F.R. § 410.32). In general, tests not ordered by the physician who is treating the beneficiary are not reasonable and necessary. See also 42 C.F.R. § 411.15(k)(1).

CMS believes that the evidence discussed above is sufficient to determine if N-13 ammonia PET is reasonable and necessary. The studies discussed above demonstrate relatively high values for sensitivity (88-97%) and specificity (90-100%). These studies are well designed and use the appropriate gold standard of angiographic findings. Also, support from the two major specialty societies, as well as testimony from key experts who attest to the fact that N-13 ammonia PET has achieved mainstream use in the practice of nuclear cardiology, provide additional evidentiary support.

Accuracy in assessing myocardial perfusion and matching it to myocardial viability studies provides crucial information to physicians attempting to select appropriate patients for revascularization. Revascularizing stenotic vessels that perfuse nonviable myocardium is not felt to be beneficial. Thus, this information allows physicians to alter patient management decisions. CMS believes that the evidence is adequate to conclude that the use of N-13 ammonia PET in clinical practice has the potential to improve net health outcomes through changes in patient management..

Although the Demer et al. study, which compares N-13 ammonia and Rb-82, fails to test both tracers head-to-head in the same population, it was sufficiently well crafted to demonstrate that both tracers have high reliability and validity in assessing myocardial perfusion. CMS believes the evidence is adequate to conclude that both N-13 ammonia PET and Rb -82 PET are of equal accuracy and reliability when used in the evaluation of myocardial perfusion.

In its 1995 decision, CMS concluded that Rb-82 PET was reasonable and necessary when used in place of but not in addition to a SPECT or following an inconclusive SPECT. We did not revisit that literature. Our literature search did not identify any new articles comparing SPECT and Rb-82 PET since that decision. Our literature review from 1990 to present also did not identify any articles comparing N-13 ammonia PET and SPECT. However, the Tamaki (1988) article directly compared the two technologies and reached similar conclusions as to the comparability of SPECT and N-13 ammonia PET as did the 1995 CMS decision with respect to Rb-82 PET and SPECT. Therefore, we believe the coverage restrictions outlined in the 1995 decision with respect to SPECT should also apply in this decision.

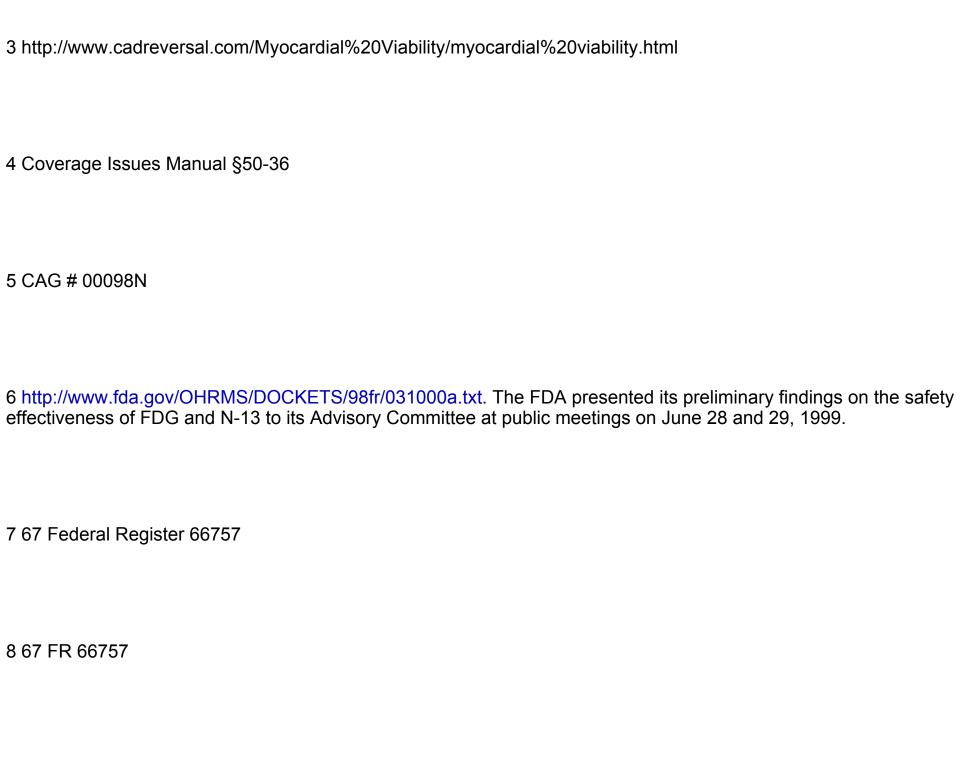
Finally, covering N-13 ammonia PET will allow communities or hospitals with access to cyclotrons to utilize PET technology in the evaluation of CAD without having to invest in the generator technology required for RB-82 PET. This will provide a diagnostic technology of at least equal accuracy at a lower investment cost to the community. Continuing to cover RB-82 PET will allow communities or hospitals that currently have access to Rb-82 generators to continue to utilize that technology, also with out additional capital investment.

#### **Decision**

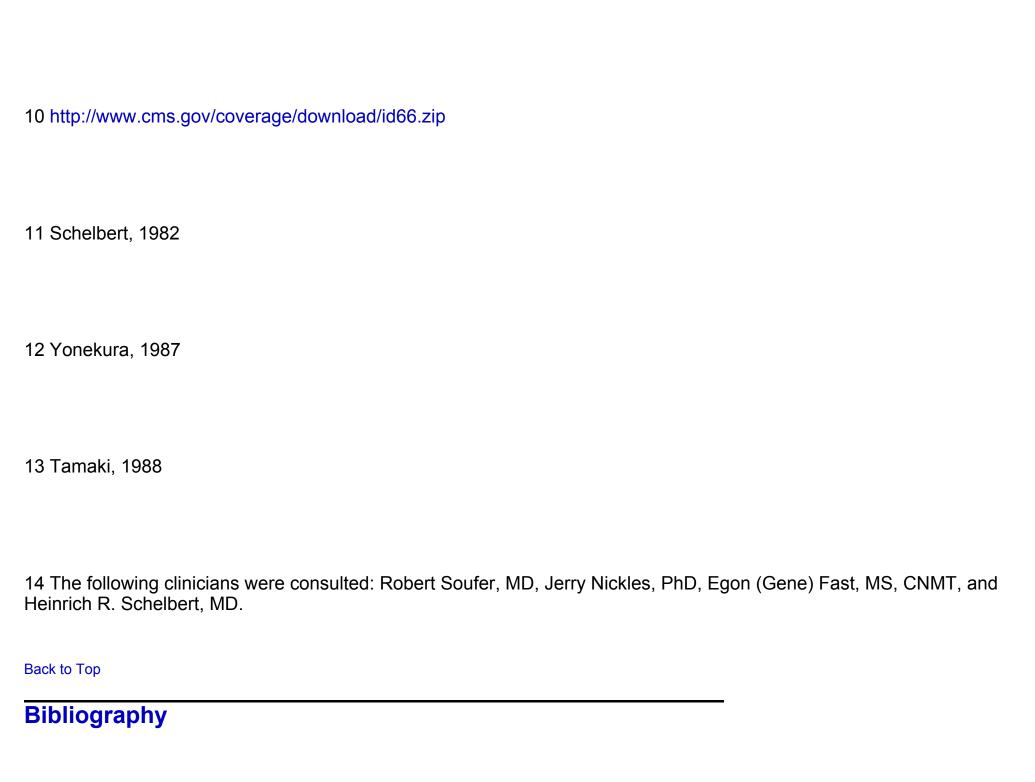
CMS determines that the evidence is adequate to conclude that the use of N-13 ammonia PET for the evaluation of myocardial perfusion is reasonable and necessary for the diagnosis or treatment of the illness or injury or to improve the functioning of a malformed body member in the population specified.

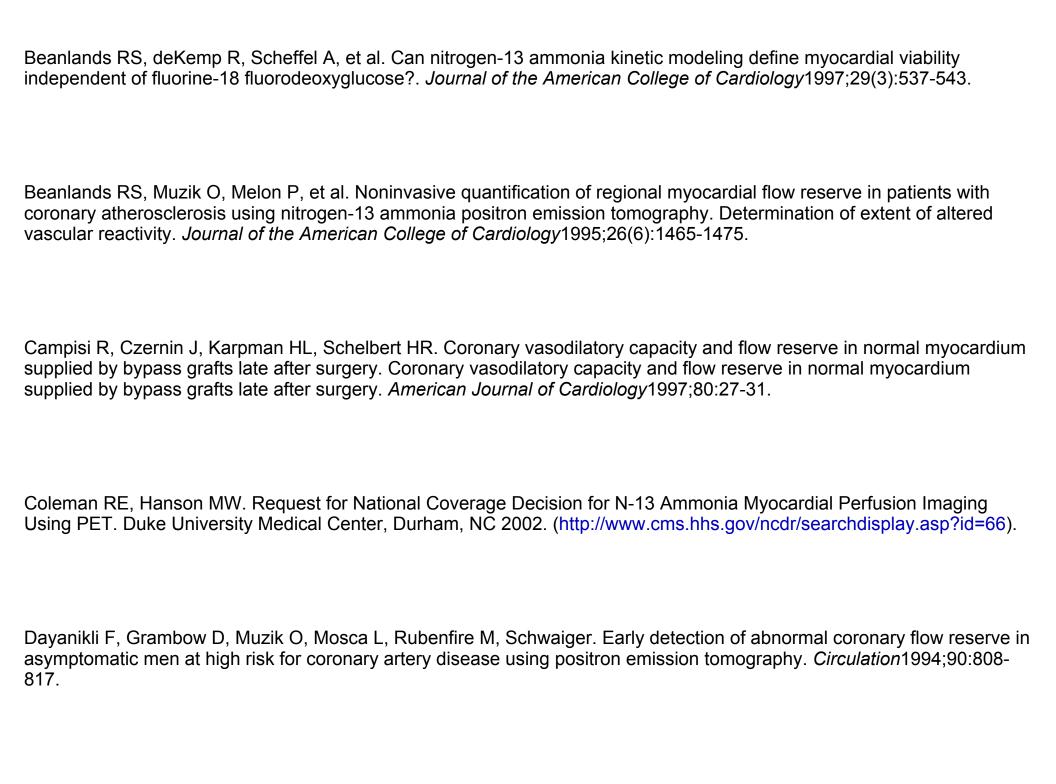
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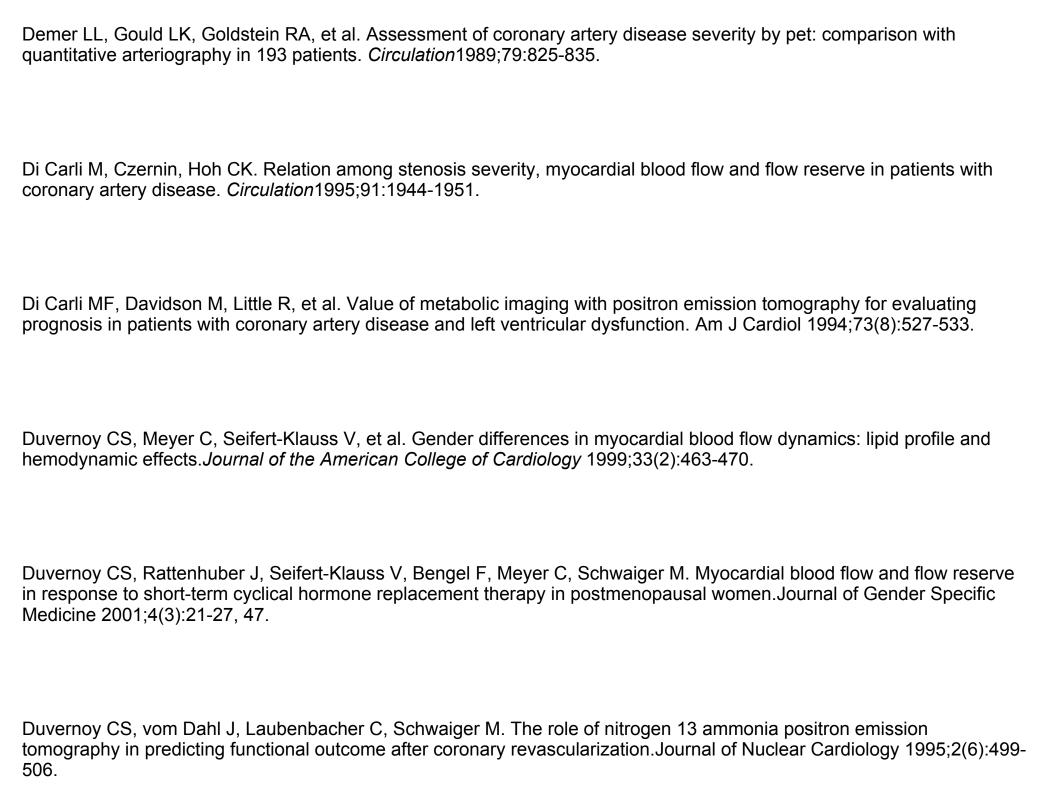
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1 American Heart Association, 2001
2 Ibid.



9 http://www.fda.gov/cder/regulatory/pet/ammonfinal.htm Printed on 3/11/2012. Page 24 of 34



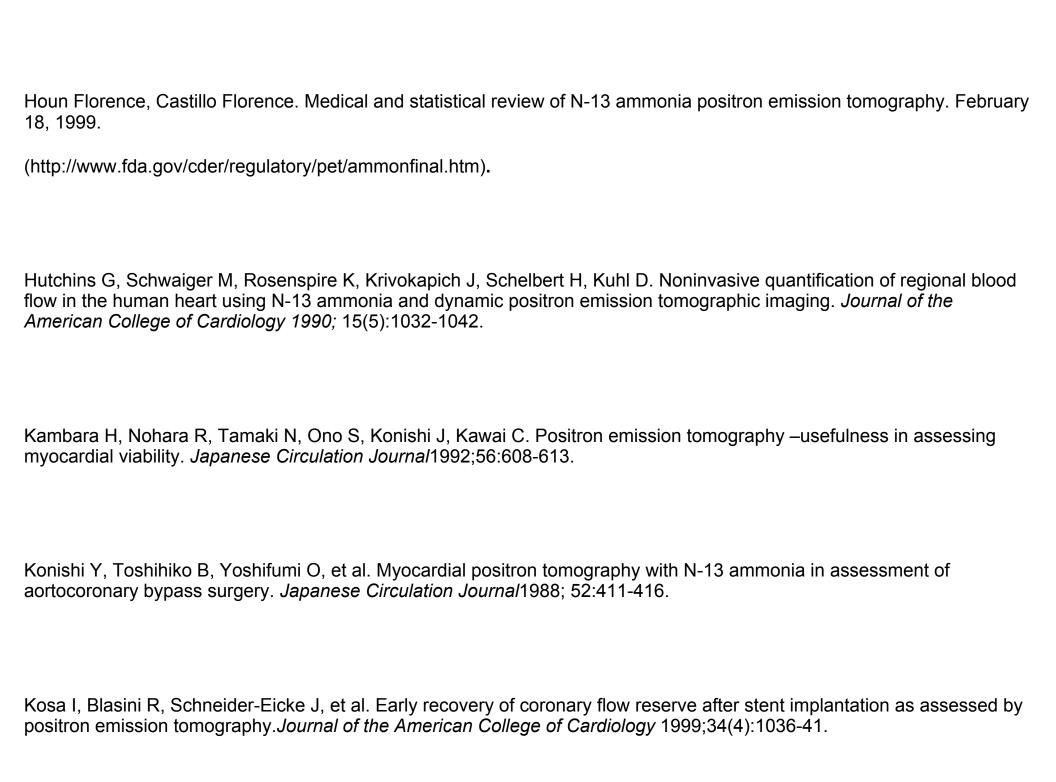


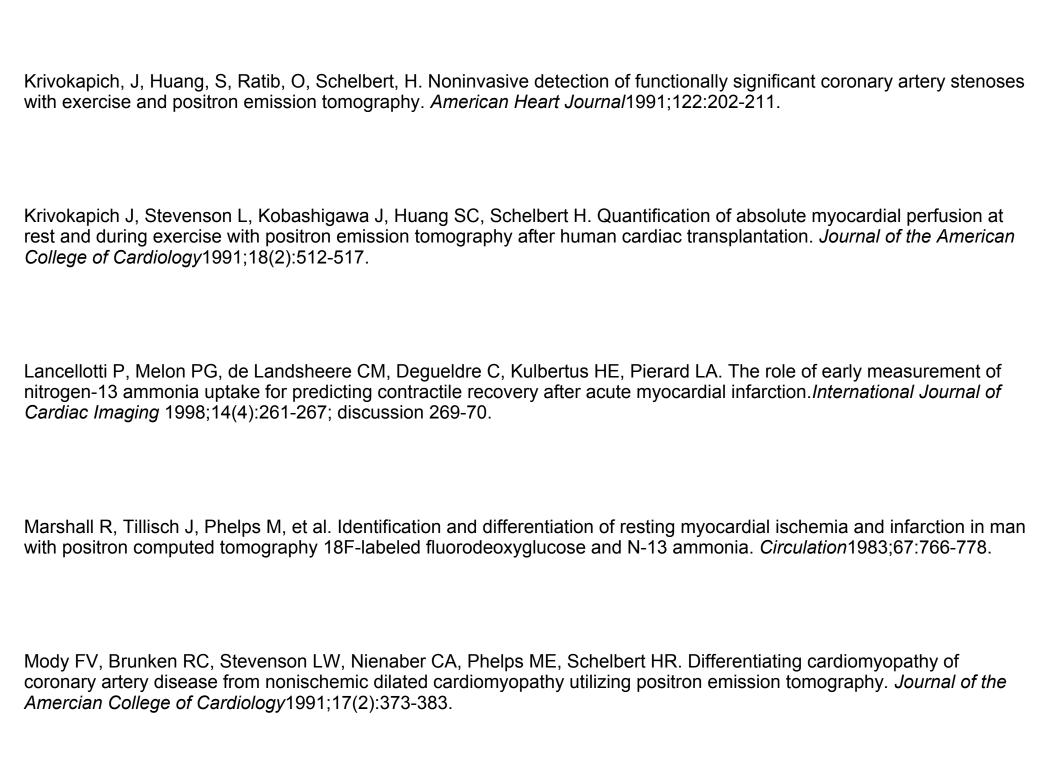


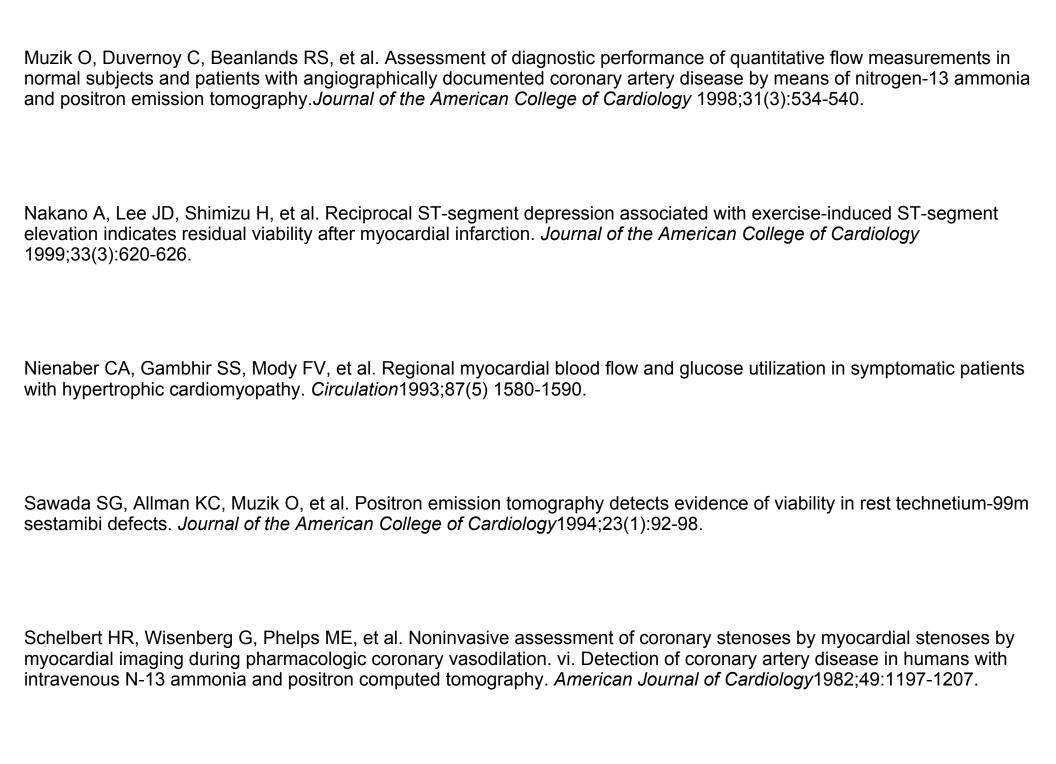
Fudo T, Kambara H, Hashimoto T, et al. F-18 deoxyglucose and stress N-13 ammonia positron emission tomography in anterior wall healed myocardial infarction. American Journal of Cardiology 1988;61(15):1191-1197. Gewirtz H, Fischman AJ, Abraham S, Gilson M, Strauss W, Alpert NM. Positron emission tomographic measurements of absolute regional myocardial blood flow permits identification of nonviable myocardium in patients with chronic myocardial infarction. Journal of the American College of Cardiology 1994;23(4):851-859. Giorgetti A, Sambuceti G, Neglia D, Parodi O. Myocardial blood flow and perfusion reserve in infarcted patients with stress -induced normalization of previously negative T waves: a positron emission tomography study. *Journal of Nuclear* Cardiology 1999;6(1 Pt 1):11-9. Gould LK, Goldstein RA, Mullani NA, et al. Noninvasive assessment of coronary artery stenoses by myocardial perfusion imaging during pharmacological coronary vasodilation. Clinical feasibility of positron cardiac imaging without a cyclotron using generator-produced rubidium-82. Journal of the American College of Cardiology 1986;7(4):775-789.

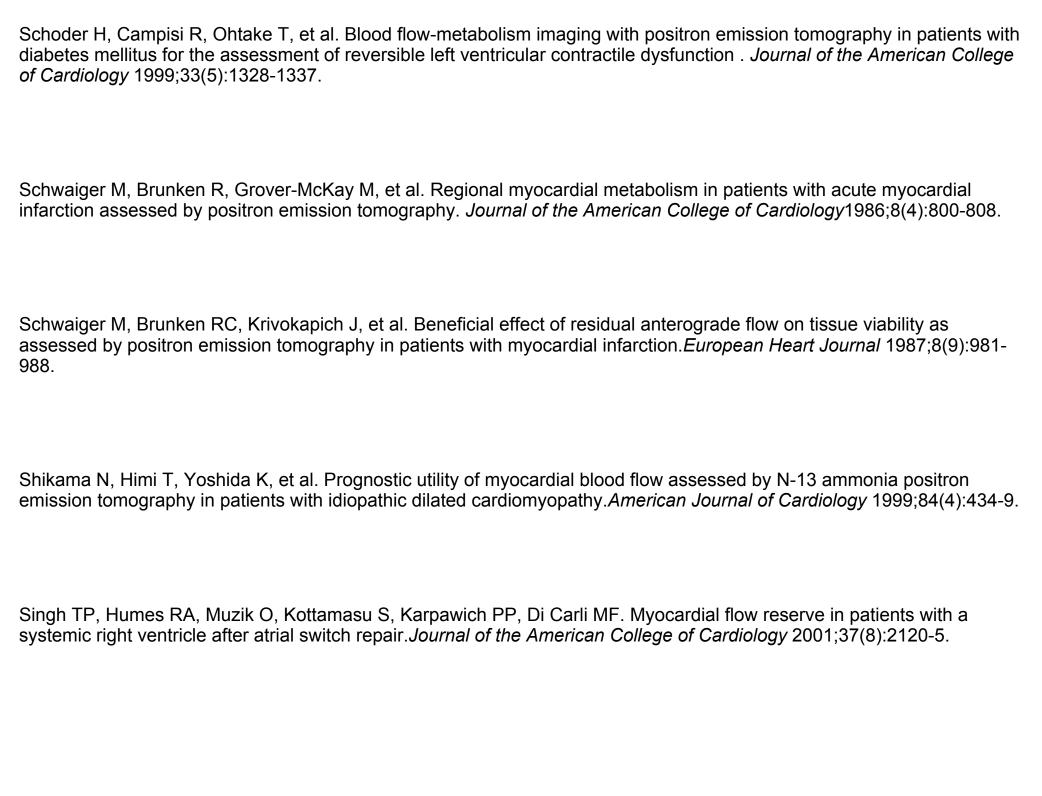
Himi T, Endo M, Yoshida K, et al. Measurements of the effect of dipyridamole on regional myocardial blood flow with

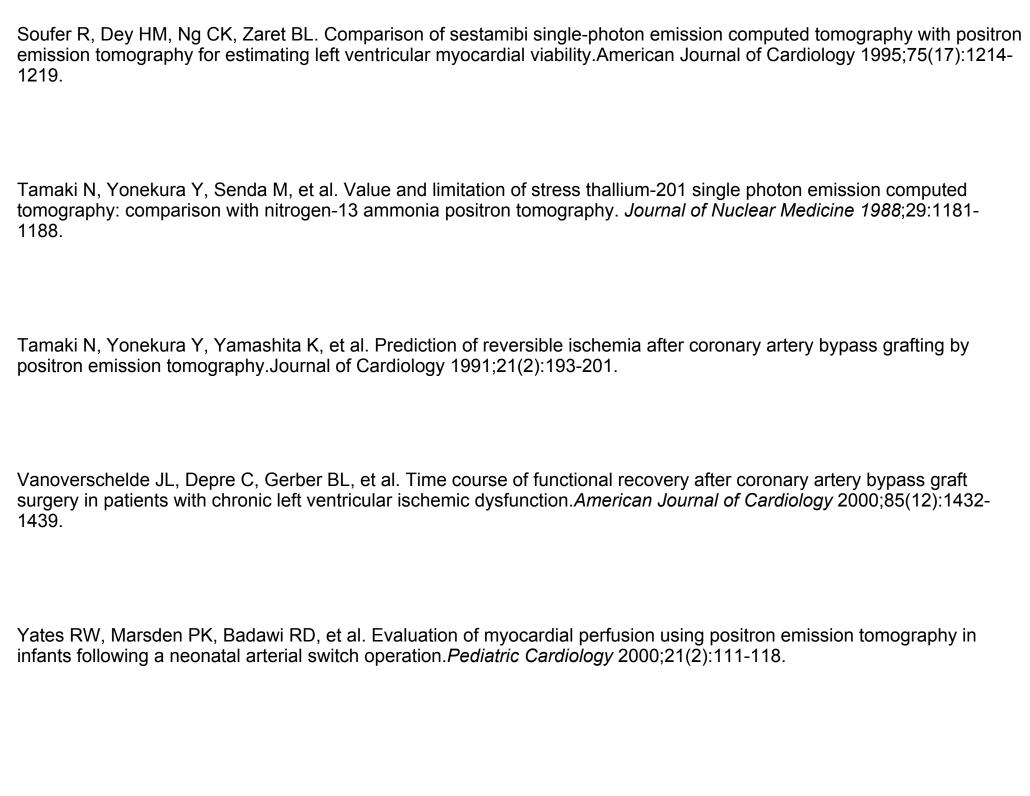
positron emission tomography and the first-pass flow model. Am J Physiol Imaging 1991;6(3):110-115.











Yonekura Y, Tamaki N, Senda M, et al. Detection of coronary artery disease with 13N-ammonia and high resolution postiron-emission computed tomography. *American Heart Journal* 1987;113(3):645-654.

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# **Related Material**

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